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BENZYLISOQUINOLINE STUDIES. PART I. OPEN-RING MODELS OF 4-BENZYLISOQUINOLINES

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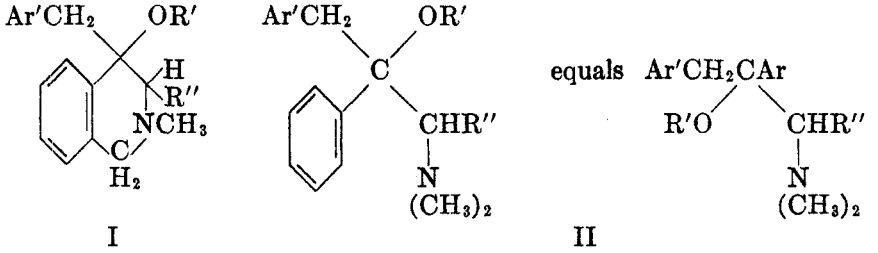
The natural alkaloids of the benzylisoquinoline group, among them morphine, contain the benzyl group in the 1-position. It appeared of interest to investigate whether the 3- and 4-benzylisoquinoline systems, respectively, have biological properties similar to these alkaloids. One derivative of 3-benzylisoquinoline, *viz.* 6,7-dimethoxy-3-(3′,4′-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline has been described by Sugasawa, Kakemi, and Kazumi (1), and some other 3- and 4-substituted isoquinolines by Whaley and Hartung (2).

In the course of this research, to which forthcoming papers will be devoted, the system (II) was studied which can be considered as a 4-benzyltetrahydroisoquinoline (I) with an opened pyridine ring (3).[1]



I II

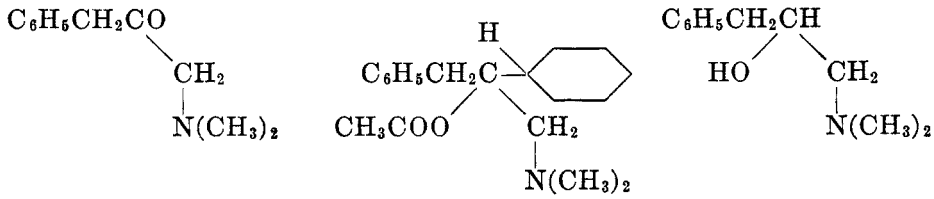
A similar trend of thought prompted the work of Kuelz, *et al.* (5), who found in the bis(phenylethyl)amines powerful analgesics; these bases are derived from the morphine molecule by opening both the nitrogen-containing heterocyclic ring and the furan system (2).

Three approaches to the synthesis of II were explored: (*a*) For R″ = H, dimethylaminoacetonitrile was a suitable starting material. It reacted with benzylmagnesium chloride (6), to give 1-phenyl-3-dimethylamino-2-propanone (III) which yielded II (Ar′ = Ar = C_6H_5, R′ = R″ = H, and Ar′ = C_6H_5, Ar = *p*-methoxyphenyl, R′ = R″ = H) upon reaction with phenyl- and *p*-methoxyphenyl-magnesium bromide, and subsequent hydrolysis, respectively. If the product of the last Grignard reaction was not hydrolyzed, but treated with acetic anhydride (7), the acetyl derivatives of the tertiary carbinols were obtained (II, R′ = CH_3CO, R″ = H).

For the purpose of comparison, III was also treated with cyclohexylmagnesium bromide, and the acetyl derivative (IV) was isolated. III could be hydrogenated catalytically to 1-phenyl-3-dimethylamino-2-propanol (V), which was also converted into the corresponding acetate. These compounds are derived

[1] Morrison and Rinderknecht (4) have prepared homologs of II, in which another methylene group is interposed between the "CHR" group of II and the nitrogen atom.

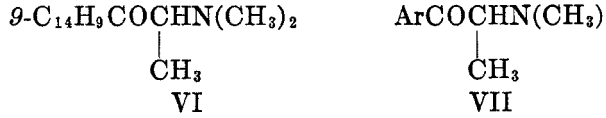
from the general formula (II), if Ar′ = C_6H_5, R″ = H, and Ar is replaced by cyclohexyl and hydrogen, respectively.



III IV V

(*b*) As Thomson and Stevens (6) have pointed out, the above reaction of dimethylaminoacetonitrile with benzylmagnesium chloride or arylmagnesium halides cannot be extended to α-dimethylaminopropionitrile or its higher homologs. Only in one case, an exception from the rule has been observed: α-dimethylaminopropionitrile gives, with 9-phenanthrylmagnesium bromide, the expected 9-(α-dimethylaminopropionyl)phenanthrene (VI), but this could not be induced to react further with benzylmagnesium chloride to II (Ar′ = phenyl, Ar = 9-phenanthryl, R′ = H, R″ = CH_3). It is interesting that also an attempt to prepare from VI the corresponding secondary alcohol, failed; 9-propylphenanthrene was obtained instead. Similar hydrogenolytic reactions have recently been described by Metayer (8).

For the synthesis of the substances of type II with R″ = CH_3, the reaction of benzylmagnesium chloride with α-dimethylaminopropiophenones (VII) proved suitable. Through the corresponding α-bromoketones, α-dimethylaminopropiophenone and its 4-methoxy-, 3,4-dimethoxy-, and 3,4-methylenedioxy derivatives were prepared; reaction with benzylmagnesium chloride afforded the following alcohols II: Ar′ = C_6H_5, R′ = H, R″ = CH_3, and Ar = phenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl or 3,4-methylenedioxyphenyl. The corresponding acetyl derivatives were prepared either by direct acetylation of the Grignard product or by acetylation of the carbinols with acetic anhydride.



VI VII

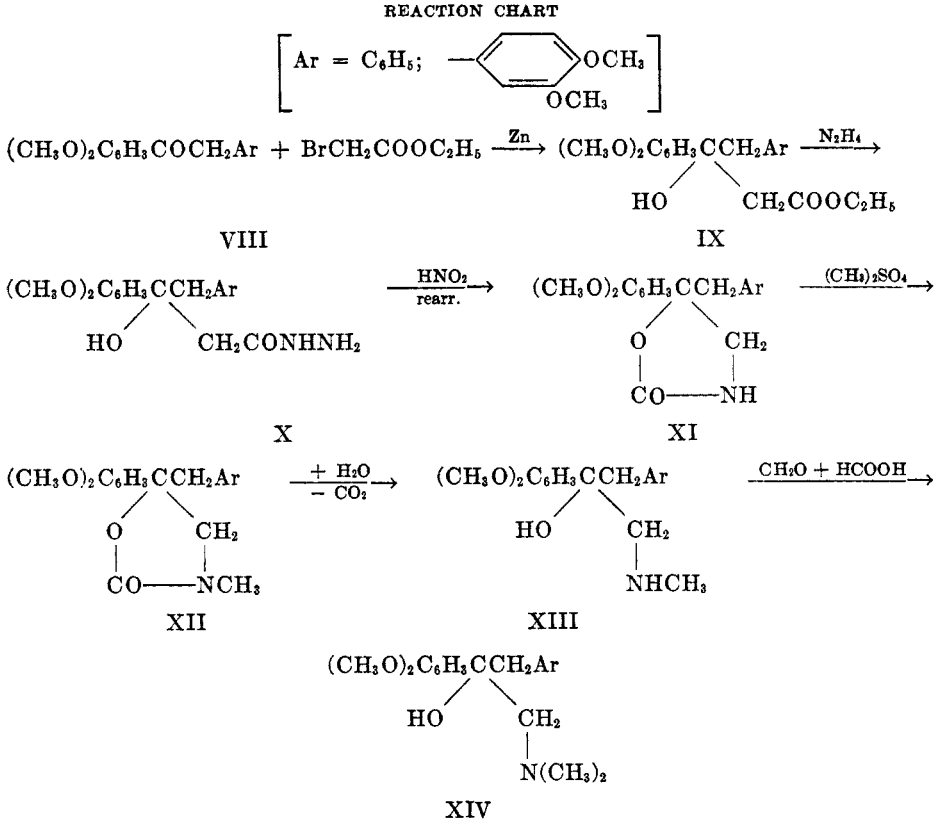
(*c*) The usefulness of this method is limited by the difficult availability of alkoxy-substituted benzylmagnesium chlorides (9–12). For the preparation of II (Ar′ = Ar = 3,4-dimethoxyphenyl, R′ = R″ = H) and—as a model experiment—for that of II (Ar = 3,4-dimethoxyphenyl, Ar′ = phenyl, R′ = R″ = H), a different method was adopted, outlined in the following Chart.

1-Phenylacetyl-3,4-dimethoxybenzene [in the second sequence: 3,4, 3′,4′-tetramethoxydesoxybenzoin (VIII)] reacted with ethyl bromoacetate to give ethyl β-hydroxy-β-(3,4-dimethoxyphenyl)-γ-phenylbutyrate (IX). When the corresponding hydrazide (X) was treated with nitrous acid and the azide decomposed in absence of water, the Curtius rearrangement was accompanied by isomerization to 5-benzyl-5-(3,4-dimethoxyphenyl)-2-oxazolidone (XI) which

was the methylated in the 3-position (XII). Hydrolysis of the ring system with liberation of carbon dioxide led to 1-phenyl-2-(3,4-dimethoxyphenyl)-3-methylamino-2-propanol (XIII), in which the nitrogen atom could be further methylated to (XIV) by formaldehyde and formic acid (13–19).

The Curtius rearrangement of β-hydroxyacid azides has been described first by Schroeter (20) and has been employed recently by Baltzly and Buck (21) and Ide and Blatzly (22). This reaction recalls another method of producing oxaxole derivatives, *viz.* the transformation of the azides of α-benzamidocinnamic and -β,β-dimethylacrylic acids, into 2-phenyl-4-benzylidene- and -4-isopropylidene-5-oxazolone (23).

REACTION CHART



In the second sequence (Ar = 3,4-dimethoxyphenyl), the last step (methylation by formic acid and formaldehyde), unexpectedly, did not give (XIV), but its dehydration product, probably α-dimethylaminomethyl-3,4,3′,4′-tetramethoxy stilbene.

Pharmacological properties. Through the courtesy of Dr. A. Krebser, a number of substances prepared in the course of the investigation were tested in the laboratories of Messrs. J. R. Geigy, Basle (Switzerland) for their analgesic and pressor activity, and were also compared with papaverine. The analgesic activity

was tested on mice; the pressor activity on cats in Numal narcosis. The comparison with papaverine was carried out using the method of Krawkow and Pissemski (rabbit's ear) (Table VI).

EXPERIMENTAL

1-Phenyl-3-dimethylamino-2-propanone (III) was prepared according to Thomson and Stevens (6) with slight modifications: to a Grignard solution, prepared from 8.7 g. of magnesium, 47.5 g. of benzyl chloride, and 200 cc. of ether, was added in an atmosphere of nitrogen and with stirring, a mixture of 17 g. of dimethylaminoacetonitrile (24) and 75 cc. of ether at −10 to 0°. Stirring was continued until the mixture reached room temperature. After 12 hours, ammonium sulfate and ice were added, the ether layer extracted with 100 cc. of 25% sulfuric acid, and the acid solution heated at 95° for one hour. It was then cooled, made alkaline with 33% sodium hydroxide solution, and after addition of an excess of potassium carbonate, extracted with ether. The ether solution was dried with potassium carbonate and distilled. B.p. 141°/26 mm.; yield, 19 g.

Picrate: crystallized from ethanol, m.p. 126–127°.

Anal. Calc'd for $C_{17}H_{18}N_4O_8$: N, 13.8. Found: N, 13.8.

1-Phenyl-3-dimethylamino-2-propanol (V). The ketone was hydrogenated in presence of Raney nickel at room temperature and atmospheric pressure. The theoretical quantity of hydrogen was absorbed in 12 hours. The product boiled at 140°/26 mm. and was characterized by its *picrate*; crystallized from ethanol, m.p. 134–135°.

Hydrochloride of the acetyl derivative of (V) (*"Substance A"*). From 1.7 g. of V with 10 cc. of benzene and 0.8 g. of acetyl chloride at 40° for 3 hours. The crystals which separated (2.1 g.), were filtered and washed with benzene. After recrystallization from acetone with some ethanol, the hydrochloride melted at 177–179°.

Anal. Calc'd for $C_{13}H_{20}ClNO_2$: C, 60.7; H, 7.8; N, 5.4.
Found: C, 60.5; H, 8.2; N, 5.4.

The reaction of 1-phenyl-3-dimethylamino-2-propanone (III) (in benzene solution) with Grignard compounds (3 mole) was carried out in a nitrogen atmosphere and at 5–10°; the reaction product was decomposed with cold ammonium sulfate solution, extracted with dilute sulfuric acid, precipitated with alkali, and taken up with ether (Table I). For the preparation of the acetyl derivatives, the product of the Grignard reaction was treated with acetic anhydride at 25° before the addition of ammonium sulfate; in this case, it was preferable to extract the base with acetic acid and to precipitate it with ammonia (method *a*). Alternatively, the aminoalcohol was acetylated with acetyl chloride in benzene solution at 40°; thus, the hydrochloride of the acetyl derivative was obtained (method *b*) (Table II).

9-(α-Dimethylaminopropionyl)phenanthrene (VI). To a Grignard reagent, prepared from 25.7 g. of 9-bromophenanthrene, 2.4 g. of magnesium, 75 cc. of ether, and 50 cc. of benzene (25), 5 g. of α-dimethylaminopropionitrile (24) in 50 cc. of benzene was added. After refluxing for 10 hours and decomposition with ammonium chloride, the filtered benzene-ether layer was heated for one hour at 95–100° with 100 cc. of 25% sulfuric acid, the solvents being distilled off simultaneously. The acid solution was then washed twice with benzene, made alkaline with 30% sodium hydroxide solution, and extracted with fresh benzene. B.p 156–160°/0.1 mm.; yield, 7.5 g.

Anal. Calc'd for $C_{19}H_{19}NO$: C, 82.3; H, 6.9.
Found: C, 82.6; H, 6.7.

Hydrochloride, from butyl acetate-methanol (5:1), m.p. 233–235°.

Anal. Calc'd for $C_{19}H_{20}ClNO$: C, 72.8; H, 6.4.
Found: C, 73.4; H, 7.1.

When an alcoholic solution of VI was shaken with hydrogen in the presence of Raney nickel until absorption ceased, and the filtrate was evaporated, there remained an oil which contained no basic substance. In the distillate, however, a volatile amine was present. The oil crystallized spontaneously and formed needles; from an ethanol-acetone mixture,

m.p. 63°. The m.p. and the analytical data show that the substance is 9-propylphenanthrene (26).

Anal. Calc'd for $C_{17}H_{16}$: C, 92.7; H, 7.3.
Found: C, 92.4; H, 7.3.

The starting materials for the *preparation of the substances* (II), in which R'' = CH_3, the α-dimethylaminopropiophenones (VII), were the corresponding propiophenones, which were brominated in acetic acid at 10–20°; *p*-methoxypropiophenone (27), 3,4-di-

TABLE I

2-SUBSTITUTED 1-PHENYL-3-DIMETHYLAMINO-2-PROPANOLS, $C_6H_5CH_2C(HO)(Ar)CH_2N(CH_3)_2$

Ar	B.P., °C./mm.	Yield, %	Picrate	M.P., °C.	Analysis					
					Calc'd			Found		
					C	H	N	C	H	N
C_6H_5	135–140/0.3	35.3	$C_{23}H_{24}N_4O_8$	175–177[a]	57.0	5.0	11.6	57.4	5.3	11.6
p-$CH_3OC_6H_4$	155/0.3[b]	15.4	$C_{24}H_{26}N_4O_9$	184–186[a]	56.0	5.0	10.9	56.1	5.4	11.0

[a] Recrystallized from alcohol. [b] Also obtained (in 85% yield) from 4-methoxy-ω-dimethylaminoacetophenone and benzylmagnesium chloride.

TABLE II

2-SUBSTITUTED 1-PHENYL-3-DIMETHYLAMINO-2-ACETOXYPROPANES, $C_6H_5CH_2C(CH_3COO)(R)CH_2N(CH_3)_2$

R	Method	B.P., (°C./mm.)	Yield, %	Picrate	M.P., °C.	Analysis						Code No.
						Calc'd			Found			
						C	H	N	C	H	N	
C_6H_5	*a*	135–140/0.3[a]	30.0	$C_{25}H_{26}N_4O_9$	155–156[b]	57.0	4.9	10.6	57.4	5.2	10.9	B
p-$CH_3OC_6H_4$	*b*	—	Quant.	$C_{26}H_{28}N_4O_{10}$	160[c]	56.0	5.0	10.9	56.1	5.4	11.0	
Cyclohexyl	*a*	135–136/0.1	18.0	$C_{25}H_{32}N_4O_9$	134–35[c]	56.4	6.0	10.5	56.5	6.0	10.7	C

[a] Hydrochloride, from ethanol-methyl ethyl ketone, m.p. 181–183°. *Anal.* Calc'd. for $C_{19}H_{24}ClNO_2$: C, 68.5; H, 7.2; N, 4.2. Found: C, 68.6; H, 7.3; N, 4.0. [b] Recrystallized from ethanol. [c] Recrystallized from ethanol-acetone.

methoxypropiophenone (28, 29), and 3,4-methylenedioxypropiophenone (30). 3,4-Methylenedioxy-α-bromopropiophenone was obtained in 60% yield; it crystallized from methanol and melted at 52–53°.

Anal. Calc'd for $C_{10}H_9BrO_3$: C, 46.6; H, 3.5; Br, 31.1.
Found: C, 46.6; H, 3.4; Br, 31.0.

The bromine was replaced by the methylamino group when the bromoketone (0.15 mole) in benzene solution was added, at 5° and with stirring, to an ethereal solution of dimethylamine (0.3 mole) over a period of 40 minutes. Stirring was continued as the temperature rose gradually to 30°. After three hours, the mixture was filtered, washed once with water, and extracted with 15% hydrochloric acid. After alkalinization, the base was extracted with ether [Table III; α-dimethylaminopropiophenone (VII, Ar = C_6H_5): (31)].

The interaction of the aminoketones listed in Table III with benzylmagnesium chloride led to the 1-phenyl-2-aryl-3-dimethylamino-2-butanols (II, R′ = H, R″ = CH_3) (Table IV). When the product of the Grignard reaction was treated with acetic anhydride (method *a*), or the isolated carbinols were acetylated with acetyl chloride (method *b*), the acetyl derivatives of these alcohols (II, R′ = CH_3CO, R″ = CH_3) were obtained, in the latter case as hydrochlorides (Table V).

TABLE III

α-DIMETHYLAMINOPROPIOPHENONES $ArCOCH(CH_3)N(CH_3)_2$

CODE NO.	Ar	B.P. (°C./MM.)	YIELD, %	HYDROCHLORIDE, M.P.	PICRATE	M.P., °C.	ANALYSIS					
							Calc'd			Found		
							C	H	N	C	H	N
D	*p*-Methoxyphenyl	135/3	81	176–178[a]	$C_{18}H_{20}N_4O_9$[b]	163	49.5	4.6	12.8	49.5	4.5	12.8
E	3,4-Dimethoxyphenyl	131/0.2	83	145–148[c, d]	$C_{19}H_{22}N_4O_{10}$[e]	156	48.9	4.7	12.0	48.9	4.5	12.4
F	3,4-Methylenedioxyphenyl	110–112/0.2	85	252–254 (decomp.)[f]	$C_{18}H_{18}N_4O_{10}$[b]	156–157	48.0	4.0	12.4	48.2	4.1	12.0

[a] After softening between 90–100°. [b] Recrystallized from ethanol. [c] Recrystallized from isopropanol. [d] Ref. 12. [e] Recrystallized from ethanol-acetone. [f] Recrystallized from ethanol-methanol.

TABLE IV

1-PHENYL-2-ARYL-3-DIMETHYLAMINO-2-BUTANOLS, $C_6H_5CH_2C(OH)(Ar)CHN(CH_3)_2$

Ar	YIELD, %	PICRATE	RECRYSTALLIZED FROM	M.P., °C.	ANALYSIS					
					Calc'd			Found		
					C	H	N	C	H	N
p-Methoxyphenyl	73	$C_{25}H_{28}N_4O_9$	Ethanol	173	56.8	5.3	10.6	56.4	5.0	10.2
3,4-Dimethoxyphenyl	85	$C_{26}H_{30}N_4O_{10}$	Ethanol-acetone	199–200	55.9	5.4	10.0	55.9	5.2	9.7
3,4-Methylenedioxyphenyl	80	$C_{25}H_{26}N_4O_{10}$	Ethanol-acetone	201	55.4	4.8	10.3	55.4	4.5	10.0

Ethyl β-hydroxy-β,γ-bis(3,4-dimethoxyphenyl)butyrate (IX, *Ar = 3,4-dimethoxyphenyl*). To 4 g. of freshly activated powdered zinc (32), there was added a little iodine and 15 cc. of a 40°-solution of 14.8 g. of 3,4,3′,4′-tetramethoxydesoxybenzoin (VIII) and 4.6 cc. of ethyl bromoacetate in 50 cc. of benzene and 10 cc. of ether. The mixture was heated with stirring until reaction set in, and the remainder of the solution added during 45 minutes. After refluxing for two hours, the reaction mixture was cooled to 5° and decomposed with 10% sulfuric acid. The ether-benzene layer was washed successively with 5% sulfuric acid, 10% sodium carbonate solution, and water, dried and evaporated *in vacuo*. The resulting thick, yellowish oil was dissolved in two parts of ether and left overnight at low temperature. The crystals (3 g.) which separated were identified as unchanged starting material. The filtrate, upon evaporation, left 14 g. (= 74%) of a thick oil which was pure enough for the next step.

TABLE V

1-PHENYL-2-ARYL-3-DIMETHYLAMINO-2-ACETOXYBUTANES, $C_6H_5CH_2CCHN(CH_3)_2$ (CH₃COO, Ar, CH₃)

CODE NO.	Ar	B.P., °C./MM.	YIELD, %	HYDROCHLORIDE	M.P., °C.	ANALYSIS						PICRATE	M.P., °C.	ANALYSIS					
						Calc'd			Found					Calc'd			Found		
						C	H	N	C	H	N			C	H	N	C	H	N
G	Phenyl	154/0.35	60[a]	$C_{20}H_{26}ClNO_2$[b]	204–205	69.2	7.5	4.0	69.4	7.0	4.3	$C_{26}H_{28}N_4O_9$[c]	182–184	57.8	5.2	10.4	58.0	5.5	10.7
H	*p*-Methoxyphenyl	152/0.3	80[d]	$C_{21}H_{28}ClNO_3$[b]	187	66.8	7.5	3.7	67.1	7.5	3.3	$C_{27}H_{30}N_4O_{10}$[f]	170	56.8	5.3	9.8	56.9	5.2	9.8
J	3,4-Dimethoxyphenyl	165/0.3	43[a] 80[d]	[g]	218–219							$C_{28}H_{32}N_4O_{11}$[f]	210	56.0	5.3	9.3	56.3	5.4	9.6
K	3,4-methylenedioxyphenyl	160–165/0.3	42[a]	[g]	218–219							$C_{27}H_{28}N_4O_{11}$[c]	181–182	55.5	4.8	9.6	55.4	5.2	9.6

[a] Method (*a*). [b] Recrystallized from ethanol-butyl acetate or acetone-methanol. [c] Recrystallized from ethanol. [d] Method (*b*). [e] Recrystallized from acetone-methanol. [f] Recrystallized from acetone-ethanol. [g] From isopropanol-methanol.

For further purification the crude ester was treated with Girard T reagent, and recrystallized from ether. M.p. 72°.

Anal. Calc'd for $C_{22}H_{28}O_7$: C, 65.3; H, 6.9.

Found: C, 65.0; H, 7.0.

The 3,4,3′,4′-tetramethoxydesoxybenzoin (VIII) was prepared either by reduction of veratroin (33) with stannous chloride (34) or from veratrole and homoveratroyl chloride (35) with aluminum chloride according to Allen and Buck (36).

β-Hydroxy-β,γ-bis(3,4-dimethoxyphenyl)butyrhydrazide (X, *Ar = 3,4-dimethoxyphenyl*). A mixture of 10.8 of the foregoing ester, 3 cc. of hydrazine hydrate and 6 cc. of methanol was refluxed for 3½ hours. To the clear solution, two parts of ether were added and the mixture was cooled for two hours. The hydrazide was collected, washed with ether-methanol (1:1) (8 g., 77%) and recrystallized from methanol. M.p. 154–155°.

Anal. Calc'd for $C_{20}H_{26}N_2O_6$: C, 61.5; H, 6.6; N, 7.2.

Found: C, 61.7; H, 6.5; N, 6.9.

5-(3,4-Dimethoxyphenyl)-5-(3,4-dimethoxybenzyl)-2-oxazolidone. (XI, *Ar = 3,4-dimethoxyphenyl*). The hydrazide (3.6 g.) was suspended in a mixture of 40 cc. of ice water and 1.5 cc. of acetic acid and an aqueous solution of 1.5 g. of sodium nitrite was added with vigorous stirring. Benzene was then added and stirring continued until the gummy mass which formed had dissolved completely. The benzene solution was filtered from a little unchanged hydrazide, dried carefully and distilled (evolution of nitrogen). The oily residue was triturated with cold benzene, containing a little petroleum ether, and filtered. Yield, 3.2 g. Needles from methanol, m.p. 161°.

Anal. Calc'd for $C_{20}H_{23}NO_6$: C, 64.4; H, 6.2; N, 3.8.

Found: C, 64.5; H, 6.2; N, 4.1.

5-(3,4-Dimethoxyphenyl)-5-(3,4-dimethoxybenzyl)-3-methyl-2-oxazolidone. (XII, *Ar = 3,4-dimethoxyphenyl*). For the methylation, 2.7 g. of the oxazolidone was added to a solution of 0.4 g. of sodium methoxide in 10 cc. of methanol. The mixture was evaporated *in vacuo* to dryness, the residue taken up with 15 cc. of toluene and the mass evaporated again. To the resulting cake, 15 cc. of toluene and 0.8 cc. of methyl sulfate was added and the mixture heated for one hour on the water-bath, after which period the reaction was neutral. The toluene solution was washed with water, dried, and evaporated *in vacuo*. The residue (2.7 g.) was triturated with ether, containing a few drops of methanol, and recrystallized from a mixture of ether and methanol. M.p. 118–120°.

Anal. Calc'd for $C_{21}H_{25}NO_6$: C, 65.1; H, 6.5; N, 3.6.

Found: C, 64.7; H, 6.1; N, 3.7.

1,2-Bis(3,4-dimethoxyphenyl)-3-methylamino-2-propanol (XIII, *Ar = 3,4-dimethoxyphenyl*). The foregoing derivative (1.5 g.) was heated at 55–60° with 4 cc. of concentrated hydrochloric acid until the evolution of carbon dioxide ceased. After addition of 25 cc. of methanol, the reaction product was concentrated *in vacuo* at 50°, and the operation was repeated. Then, the resulting syrup was successively triturated with ether and acetone and gave a crystalline powder (0.4 g.) of m.p. 220–222°. The *free base* had m.p. 105° and is characterized by a well-defined *picrate*, from acetone-alcohol mixture, m.p. 184°.

Anal. Calc'd for $C_{26}H_{30}N_4O_{12}$: C, 52.9; H, 5.1; N, 9.5.

Found: C, 52.5; H, 5.2; N, 9.8.

α-Dimethylaminomethyl-3,4,3′,4′-tetramethoxystilbene (?). When 0.5 g. of the above base, m.p. 105°, was added to a mixture of 0.3 cc. of formalin solution and 0.2 cc. of formic acid, effervescence set in at once. The reaction was completed by heating at 80° for thirty minutes. The product was converted into its *picrate*, by treatment with alcoholic picric acid solution. From alcohol-acetone mixture, m.p. 188–189°.

Anal. Calc'd for $C_{27}H_{30}N_4O_{11}$: C, 55.3; H, 5.1; N, 9.5.

Found: C, 55.5; H, 5.3; N, 9.3.

β-Hydroxy-β-(3,4-dimethoxyphenyl)-γ-phenylbutyrhydrazide (X, *Ar = C_6H_5*). From 1-phenylacetyl-3,4-dimethoxybenzene (VIII, Ar = C_6H_5) (37), the ester (IX, Ar = C_6H_5) was prepared, as described above, in 76% yield, and the crude oily compound converted into the hydrazide. Yield, 70%. It crystallized from methanol, m.p. 88°.

Anal. Calc'd for $C_{18}H_{22}N_2O_4$: C, 65.5; H, 6.6; N, 8.5.
Found: C, 65.4; H, 6.7; N, 8.7.

The hydrazide is easily soluble in acetone, but after a few minutes, the *isopropylidene-hydrazide* crystallized; such reactions of hydrazides with ketones have been described before by Curtius and co-workers (38). After recrystallization from methanol, the product melted at 137–139°.

Anal. Calc'd for $C_{21}H_{26}N_2O_4$: C, 68.0; H, 7.0; N, 7.5.
Found: C, 68.1; H, 7.2; N, 7.1.

TABLE VI

PHARMACOLOGICAL PROPERTIES OF SUBSTANCES PREPARED

CODE NUMBER OF SUBSTANCE	ANALGESIC ACTION ON THE MOUSE, MG./KG.		COMPARISON WITH PAPAVERINE(= 1)	PRESSOR ACTIVITY, MG./KG.	
A	50	0	1:117	5	0
				10	positive
B	50	0	1:80		
C	50	0	1:200		
D	50	0	1:55.5	3	0
				10	positive
E	50	0	1:23		
	100	0			
F	50	0	1:122	5	0
	100	0			
G	50	0		3	positive
H	50	0		1	0
				>3	positive
J	50	0	1:204	3	0
K	50	0	1:172		
	100				

1-Phenyl-2-(3,4-dimethoxyphenyl)-3-dimethylamino-2-propanol (XIV, $Ar = C_6H_5$). The above described sequence of reactions was carried out with the foregoing hydrazide (3 g.). The *oxazolidone* which was formed by rearrangement of the azide, crystallized from methanol and had m.p. 148°.

Anal. Calc'd for $C_{18}H_{19}NO_4$: C, 69.0; H, 6.1; N, 4.5.
Found: C, 69.0; H, 6.3; N, 4.8.

The eventually resulting tertiary amine gave a *picrate* of m.p. 219–220°, after recrystallization from ethanol-acetone mixture.

Anal. Calc'd for $C_{25}H_{25}N_4O_{10}$: C, 55.2; H, 5.2; N, 10.3.
Found: C, 55.7; H, 5.2; N, 10.6.

SUMMARY

1. 1-Phenyl-3-dimethylamino-2-propanone (III), available from dimethylaminoacetonitrile and benzylmagnesium chloride, was converted into alcohols of type II by reaction with phenyl-, *p*-methoxyphenyl-, and cyclohexyl-magnesium bromide, and by catalytic hydrogenation.

2. In accordance with previous observations, α-dimethylaminopropionitrile does not react normally with aryl- and aralkyl-magnesium halides. Only 9-phenathrylmagnesium bromide was found to give the corresponding ketone (VI).

3. From α-dimethylaminopropiophenone, its 4-methoxy-, 3,4-dimethoxy-, and

3,4-methylenedioxy-derivatives, tertiary carbinols of type II were synthesized by means of benzylmagnesium chloride.

4. A third method leading to II consists in the Curtius rearrangement of the azides of the β-hydroxyacids, which are available by reaction of ethyl bromoacetate and zinc with suitably substituted dexsoxybenzoins. This arrangement leads to oxazolidones (XI) which can be N-methylated and which are hydrolyzed (with loss of carbon dioxide) to N-methylamines of the desired type II.

5. The pharmacological properties of the substances prepared are reported.

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